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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/917,789	07/31/2001	Gary Lynch	1819.0030002/MAC	1493

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,789	LYNCH ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-94* is/are pending in the application.

4a) Of the above claim(s) *13-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9, 10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-12) drawn to a method of determining the effect of a substance on neuronal damage induced by disruptors of lysosomal activity or induces of cathepsin D in Paper No. 13 (13 November 2002) is acknowledged. The traversal is on the ground(s) that a search and examination of all 7 Groups does not represent a burden on the Examiner. This is not found persuasive because each of the 7 Groups represents a distinct and independent invention requiring a separate and non-overlapping search and examination presenting a burden on the Examiner. However, the species requirement of Paper No. 7 (20 September 2002) is hereby *withdrawn* but the restriction between Groups I-VII is maintained. Group I will be examined to the full extent of claims 1-12 including all aforementioned species. Claims 13-94 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected material, there being no allowable generic or linking claim. The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

2. Claims 1-12 are under examination and claims 13-94 are withdrawn from consideration.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Specification

4. This application is in condition for allowance except for the following formal matters:

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. The disclosure is objected to because of the following informalities: define "AT8-ir" (pp. 13 paragraph 0041); use superscript for mutation designation for transgenic mice "C57BL/6J-ApoE^{tm1Unc}" (though out specification); designate portions of figures using letters i.e. "6A" and "6B" not "left" and "right" (Figures 6, 10-16). Appropriate correction is required.

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (pp. 25 paragraph 0080). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a screening method for substances that affect characteristics indicative of Alzheimer's disease using brain slices *in vitro* or a mouse model using lysosomal inhibitors to create the conditions under which the method is carried out, does not reasonably provide enablement for a screening method of any or all neurodegenerative diseases, use of animal

models other than mice (i.e. humans), or "conditions" other than the claimed lysosomal inhibitors (i.e. freezing the brain cells, extreme age in the mice). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claims 1-12 are directed to a method of determining the effects of a substance on characteristics of neurodegenerative disease in brain cells.

9. The specification teaches that lysosomal enzyme inhibitors such as chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid can be used to create Alzheimer like symptoms in a brain slice *in vitro* or a transgenic mouse model.

10. The art teaches that neurofibrillary tangles, phosphorylated tau, tau fragments, increased production and/or release of TGF-β, IL-1b, TNF, increased microglia reaction and/or activation, brain inflammation, conversion of p35 to p25, and increased activity of cyclin dependent protein kinase 5 (cdk5) are found in Alzheimer's patients and/or AD mouse models [Yong et al. (1999) "Lysosomal Dysfunction Results in Lamina-Specific Meganeurite Formation but Not Apoptosis in Frontal Cortex." Experimental Neurology 157: 150-160 (**IDS #AR17**); Patrick et al. (9 December 1999) "Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration." Nature 402: 615-622 (**IDS #AT11**); Kenessey et al. (1997) "Degradation of Tau by Lysosomal Enzyme Cathepsin D: Implication for Alzheimer Neurofibrillary Degeneration." Journal of Neurochemistry 69: 2026-2038; Rogers et al. (1996) "Inflammation and Alzheimer's Disease Pathogenesis" Neurobiology of Aging 17(5): 681-686 (**IDS #AR13**); WO 00/21550; Ahliganian et al. (14 March 2000) "Hyperphosphorylated tau and neurofilament

and cytoskeletal disruptions in mice overexpressing human p25, an activator of cdk5." PNAS 97(6): 2910-2915 (**IDS # AR3**); Eikelenboom et al. (1998) "Inflammation and Alzheimer's disease: Relationships between Pathogenic Mechanisms and Clinical Expression." Experimental Neurology 154: 89-98 (**IDS # AR7**).

11. While the specification is enabling for the claimed method when using *in vitro* brain slices and mouse models of Alzheimer's disease, no working examples are given re: other neurodegenerative diseases, non-mouse models.

12. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

13. Regarding neurodegenerative diseases, the art recognizes the enormous range of disorders and diseases that constitute neurodegenerative diseases including but not limited to Parkinson's disease, Huntington disease, spinocerebellular ataxias (SCA1, SCA6, SCA7), amyotrophic lateral sclerosis (ALS), and multiple sclerosis. Each neurodegenerative disease and/or disorder is caused by a distinct and independent mechanism such as a expansion of the CAG repeat in the IT15 gene in Huntington's disease versus a loss of myleination of neurons in multiple sclerosis or is of unknown mechanism as in the case of Parkinson's disease. Due to the large quantity of experimentation necessary to evaluate all neurodegenerative diseases and their signs and symptoms, the lack of direction/guidance presented in the specification regarding study of all neurodegenerative diseases, the absence of working examples directed to models other than Alzheimer's disease, the complex nature of the invention, the unpredictability of effects any given substance would have on a model for any given neurodegenerative disease [Dyment et al.

(1997) "Genetics of multiple sclerosis." Human Molecular Genetics 6(10): 1693-1698; Kirkitadze et al. (2002) "Paradigm Shifts in Alzheimer's disease and other neurodegenerative disorders: The emerging role of oliogomeric assemblies." Journal of Neuroscience Research 69: 567-577; Monani et al. "Animal models of spinal muscular atrophy." Human Molecular Genetics 9(16): 2451-2457; Orr and Zoghbi (2001) "SCA1 molecular genetics: a history of a 13 year collaboration against glutamines." Human Molecular Genetics 10(20): 2307-2311], and the breadth of the claims which fail to recite limitations which types of neurodegenerative diseases, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. Regarding conditions that disrupt lysosomal activity, the art recognizes that several conditions can disrupt lysosomal activity. Due to the large quantity of experimentation necessary to identify all applicable conditions, the lack of direction/guidance presented in the specification regarding evaluating all the applicable conditions and their effects on the claimed models of mice and *in vitro* brain slices, the absence of working examples directed to the conditions other than lysosomal enzyme inhibitor treatment, the complex nature of the invention, the unpredictability of the various conditions on lysosomal activity [Bi et al. (August 1999) "Lysosomal protease inhibitors induce meganeurites and tangle-like structures in entorinohippocampal regions vulnerable to Alzheimer's disease." Experimental Neurology 158: 312-327], and the breadth of the claims which fail to recite limitations for what constitutes a condition that disrupts lysosomal activity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Furthermore, it is not clear from the specification or the prior art as to what conditions are necessary to induce the characteristics listed in claim 1 in a healthy human subject without causing irreparable damage.

16. Thus the claimed invention is directed to a method screening for substances which effect characteristics of Alzheimer's disease , which is contrary to the teachings of the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: expectation of recovery of a human subject used to practice the claimed method, expectation of success for non-Alzheimer's disease models, would a substance that affects AD characteristics be deleterious in other neurodegenerative disease models, are the characteristics listed in claim 1 present in any other neurodegenerative disease models or patients (humans)? The specification does not provide guidance on how to overcome expected obstacles. Due to the large quantity of experimentation required to determine how to administer any given substance without doing harm to achieve an effect on a human subject, the specification's lack of guidance regarding how to overcome expected obstacles, the lack of working examples directed to all neurodegenerative diseases, the contrary state of the art, the unpredictability of what is needed to overcome the obstacles, and the large breadth of the claims, undue experimentation would be required of the skilled artisan to practice the claimed methods.

17. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step which indicates wherein a substance that affects one or all of the characteristics listed in (1)-(9) indicates that it has an affect on Alzheimer's disease.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

19. Claims 1, 3, 4, 5, 6, 7, 8, and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Bi et al. (21 March 2000) "Novel Cathepsin D Inhibitors Block the formation of Hyperphosphorylated Tau fragments in Hippocampus." Journal of Neurochemistry 74(4): 1469-1477.

20. Bi et al. (2000) teaches that treatment of organotypic hippocamal slices with lysosomal inhibitors such as ZPAD, chloroquine, and exogenous amyloid cause the accumulation of carboxy-terminal fragments of amyloid precursor protein, phosphorylated tau, and phosphorylated tau fragments thus meeting the limitations of claims 1, 3, 4, 5, 6, 7, 8, and 9 (pp. 1471; Fig. 1 and Fig. 2). Furthermore, Bi et al. (2000) teaches the successful identification of three novel cathepsin D inhibitors which block the formation of hyperphosphorylated tau fragments in the hippocamal slice cultures thus meeting the limitations of claim 1 (Table 1; Fig. 1, 3, and 4).

Summary

21. Claims 1-12 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher J. Nichols whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
February 20, 2003